Amendments to the Specification:

Replace the original Sequence Listing with the substitute Sequence Listing filed herewith.

*Please amend the paragraph **[0014]** beginning at page 4, as follows:*

Figures 1A-1EEE provide the atomic structural coordinates for BACE and the APP inhibitor peptide (SEQ ID NO:7) and (SEQ ID NO:3) as derived by X-ray diffraction of a crystal of the BACE and APP inhibitor peptide complex. "Atom type" refers to the atom whose coordinates are being measured. "Residue" refers to the type of residue of which each measured atom is a part – *i.e.*, amino acid, cofactor, ligand or solvent. The "x, y and z" coordinates indicate the Cartesian coordinates of each measured atom's location in the unit cell (Å). "Occ" indicates the occupancy factor. "B" indicates the "B-value", which is a measure of how mobile the atom is in the atomic structure ($Å^2$).

*Please amend the paragraph **[0016]** beginning at page 5, as follows:*

Unless otherwise noted, "BACE" is Beta-site APP Cleaving Enzyme, and is the β-secretase enzyme that cleaves β-amyloid precursor protein (APP) at residue 671 (770aa isoform of APP numbering). After cleavage of APP by BACE, the remaining APP is cleaved at residue 716 by γ-secretase, leaving a 42 amino acid fragment of APP that is found in the proteinaceous plaques of Alzheimer's patients. The amino acid sequence of BACE preferably has the amino acid sequence deposited with Swiss Prot under accession number P56817 (SEQ ID NO:1), including conservative substitutions. As used herein, BACE also includes "BACE peptides," which are molecules having less than the complete amino acid sequence of BACE. Preferably, BACE peptides include the active site in which BACE binds to and cleaves APP. Most preferably, the BACE peptide corresponds to amino acid residues 58-447 set forth in 1A-1EEE ("$BACE_{58-447}$)" (SEQ ID NO:7), including conservative substitutions.

*Please amend the paragraph **[0047]** beginning at page 16, as follows:*

Structure Determination and Overall Fold. Full length BACE was expressed in CHO cells as a fc fusion protein and, after purification, cleavage and partial deglycosylation, complexed

with peptide inhibitor and crystallized. Crystals diffracted to 2.3 Å and the structure was solved using the technique of molecular replacement. The search model used was derived from cod atlantic Pepsin and contained 63% of the final number of atoms. The density modified maps obtained using a poly-alanine version of the search model (39% of the final atoms) provided sufficient information to build all but 12 amino acids. The final model contains residues from 59 to 448 (SEQ ID NO:8) (using full length numbering), all 9 residues of the statine inhibitor and 360 water molecules. Of the four predicted N-linked glycosylation sites only two have interpretable electron density.

*Please amend the paragraph **[0048]** beginning at page 16, as follows:*

The overall shape of the BACE protein is spherical and is composed of two distinct domains, an N-terminal (58-207) (SEQ ID NO:9) and a C-terminal (208-447) (SEQ ID NO:10). With the first thirteen amino acids (58-71) (SEQ ID NO:11) being packed against residues 238-243 (SEQ ID NO:12). There is a significant cleft-like channel across one surface of the interface between the domains. This contains the inhibitor peptide and conserved aspartic acid motifs that define the active sites of aspartic proteases.

*Please amend the paragraph **[0049]** beginning at page 17, as follows:*

The N-terminal domain is composed of a single .alpha.-helix preceeding the loop joining the two domains and thirteen β-strands. The larger C-terminal domain has a total of seventeen β-strands and three ά-helices. The overall topology is characterised by an eight stranded antiparallel interdomain β-sheet. This central sheet comprises the majority of the active site residues including the two conserved aspartates (one from each domain:93 and 289). Asp93 and Asp289 define the position of a pseudo two-fold axis for the central β-sheet. Outside of this symmetry the two domains differ significantly. The N-terminal domain has an extra two strands extending the central sheet. In addition, there are two anti-parallel β-sheets above and below the central sheet composed of three and four β-strands respectively. Residues from the upper sheet (131-135 (SEQ ID NO:13)) fold over the active site aspartates and form a `flap` over the centre of the peptide binding cleft.

*Please amend the paragraph **[0050]** beginning at page 17, as follows:*

The C-terminal domain contains two lobes in addition to the strands which from the central β-sheet. These are weakly homologous to known aspartic protease structures. The binding pocket for the P1' and P3' positions are instead derived from three β-turns 388-391 (SEQ ID NO:14), 284-286 and 255-261 (SEQ ID NO:15).